

Transaminitis as a predictor of poor clinical outcomes in pregnant patients infected with COVID-19: retrospective case series

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Abstract

Objective: The objective of this study is to identify the effects of Coronavirus Disease 2019 (COVID-19) on liver enzymes in pregnant patients and to determine the significance of transaminitis as a predictor of worse clinical outcomes. **Design:** Case series. **Setting:** Tertiary care medical center. **Population:** 31 pregnant patients with a positive COVID-19 polymerase chain reaction (PCR) test and 20 infants who presented during March 25, 2020, to May 26, 2020. **Methods:** Maternal and neonatal outcomes were compared between patients with transaminitis and without transaminitis using one tailed Mann-Whitney test for nonparametric data and the fisher's exact test for categorical data. **Main outcome measures:** Worse maternal outcomes between the groups were defined as need for intubation, oxygen supplementation, intensive care unit (ICU) admission, maternal death, and length of hospital stay. **Results:** Of the 31 patients with COVID-19, 10/29 (34.5%) were found to have transaminitis. The patients with transaminitis had increased oxygen requirements, increased rate of intubation and ICU admissions. Neonatal outcomes in patients with transaminitis included earlier gestational age at delivery and lower birth weights, but neither were statistically significant. **Conclusion:** Our study revealed that patients with COVID-19 and concomitant transaminitis had worse clinical outcomes in the mother when compared to those without transaminitis. Further studies should be conducted to explore this link between abnormal liver studies and poor outcomes in pregnant patients diagnosed with COVID-19. **Keywords:** Coronavirus, COVID-19, transaminitis, pregnancy **Tweetable abstract:** Pregnant patients with COVID-19 and transaminitis had worse outcomes than ones without transaminitis.

Introduction:

Coronavirus Disease 2019 (COVID-19), a respiratory virus caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first discovered in Wuhan, China in December 2019 after several citizens developed symptoms of atypical pneumonia. The novel coronavirus was quick to spread throughout China and the world, research is still developing regarding its transmission and pathophysiology. On January 19, 2020 the first confirmed case of COVID-19 was documented in the United States in Washington State¹ and in March 2020 the World Health Organization (WHO) declared COVID-19 a worldwide pandemic.²

As more individuals have become infected with COVID-19, more information has surfaced regarding symptomatology and associated lab abnormalities. One association that is seen in varying degree is transaminitis in COVID-19 positive patients.³ Currently, there is limited literature describing how transaminitis may be an important predictor of clinical outcomes in pregnant patients diagnosed with COVID-19. Additionally, patients who experience these laboratory abnormalities often begin to experience deterioration in their clinical status suggested by an increase in oxygen requirement, increasing respiratory rate, need for intubation, need for urgent delivery and ICU admission.⁴

The purpose of this retrospective case series is to better understand the relationship between transaminitis

and maternal and neonatal outcomes in pregnant patients infected with COVID-19. Establishing an association between these factors can provide physicians with insight into the predictive power of these laboratory abnormalities for clinical disease progression.

Methods:

This was a case series at Westchester Medical Center, a tertiary care center located in Valhalla, New York, to compare maternal and neonatal outcomes between pregnant patients hospitalized with COVID-19, with and without transaminitis from March 25, 2020 to May 26th, 2020. This timeframe represents the initial peak of the pandemic in New York and was used to obtain preliminary data.

Data for this study was obtained from electronic medical records used at Westchester Medical Center and this project was approved by New York Medical College and Westchester Medical College Institutional Review Board (IRB). No funding was involved for this research.

All antepartum or postpartum patients diagnosed with COVID-19 who presented to Westchester Medical Center between March 25th, 2020 and May 26th, 2020 were screened for inclusion criteria. Patients who presented with COVID-19-like symptoms or those admitted for any obstetrical reason were all routinely screened and tested for COVID-19. The patients who tested positive for COVID-19 were then separated into two groups: patients with COVID-19 who had transaminitis at any point in their hospital course, and patients with COVID-19 without transaminitis. For the study, transaminitis was defined as aspartate transaminase (AST) > 35 U/L and alanine transaminase (ALT) > 55 U/L according to Westchester Medical Center's laboratory reference range.

Patients with transaminitis who had a history of hepatitis, transaminitis of any etiology diagnosed before COVID-19 diagnosis, a diagnosed liver mass, HELLP syndrome or preeclampsia during current pregnancy, current diagnosis of cholelithiasis, or intrahepatic cholestasis of pregnancy, or a history of alcohol abuse or IV drug abuse were excluded from the study.

The primary outcome for the study was maternal ICU admission. Secondary outcomes included maternal and neonatal outcomes and laboratory values. Maternal outcomes were length of hospital stay, maternal death, supplemental oxygen requirement, intubation and need for cesarean delivery. Neonatal outcomes were birth weight, Apgar score <7 at 5 minutes of life, arterial cord blood acidosis (pH <7.2), preterm delivery and gestational age (GA) at delivery. Laboratory values of interest included AST, ALT, BUN, creatinine and glucose.

Data analysis was performed using SPSS version 'X' (IBM, Inc., Armonk New York). Continuous variables are presented as medians and interquartile ranges. Categorical variables are presented as frequencies, rates and percentages. The one tailed Mann-Whitney test was used for nonparametric data and the fisher's exact test was used for categorical data. Statistical significance was defined as a p-value < 0.05.

Results:

A total of 31 patients diagnosed with COVID-19 were identified in this study; however 2 patients did not have laboratory studies performed and were thus excluded. Additionally, one patient with transaminitis was found to have preeclampsia with severe features resulting in liver abnormalities, and therefore was excluded from review. Thus, 28 patients were included in the study; 9 patients were found to be COVID-19 positive with transaminitis and 19 patients were found to be COVID-19 positive without transaminitis. Additionally, infant outcomes were reviewed for patients who delivered at Westchester Medical Center. A total of 20 infants were included, including one set of twins and one intrauterine fetal demise (IUFD), both of which were in the transaminitis group. The additional infants' statuses remained unknown and were presumed to have been delivered outside of Westchester Medical Center.

Laboratory values are listed in Table 1. The median AST level in the transaminitis group was 80.33 (45.28-100.75) and the median AST in the non-transaminitis group was 20.00 (18.18-26.42) (p <0.001). Additionally, the median ALT level for the transaminitis group was 79.73 (65.83-116.67) compared to 13.09 (10.25-27.25)

in the non-transaminitis group. ($p < 0.001$). There were no significant findings between the two groups for other laboratory values, including glucose, BUN and creatinine.

Maternal outcomes are shown in Table 2. The primary outcome of maternal ICU admission was found to be statistically significant, with more patients in the transaminitis group admitted to the ICU. 3/9 (33.3%) of transaminitis patients versus 0/19 (0.0%) of the non-transaminitis patients ($p = 0.026$) were admitted to the ICU. Significant secondary maternal outcomes included intubation and oxygen supplementation. 3/9 (33.3%) of patients in the transaminitis group were intubated while 0/19 (0.0%) of patients in the non-transaminitis group were intubated ($p = 0.026$). 6/9 (66.7%) of patients in the transaminitis group required oxygen supplementation while only 1/19 (5.3%) of patients in the non-transaminitis group required oxygen supplementation ($p = 0.001$). No maternal deaths were noted in either group. Patients with transaminitis stayed in the hospital longer than those without transaminitis, but this was not statistically significant (7.0 vs 3.0 days; $p = 0.058$). Finally, mode of delivery showed 6/7 (85.7%) patients in the transaminitis group were delivered by cesarean compared to 6/12 (50.0%) patients in the non-transaminitis group ($p = 0.173$).

None of the neonatal outcomes were found to have a statistically significant difference between the two groups (Table 3). The transaminitis group had a higher rate of preterm delivery, but this was not statistically significant. 3/8 (37.5%) patients in the transaminitis group experienced a preterm delivery with a median GA at delivery of 259.0 (228.0-263.5) days compared to 4/12 (33.3%) patients in the non-transaminitis group who experienced a preterm delivery with a median GA at delivery of 273.0 (242.3-274.0) days ($p = 0.127$). Median birth weight in the transaminitis group was also lower in the transaminitis group, 2730.0 (2509.5-3085.0) grams compared to 3225.0 (2600.0-3457.5) grams ($p = 0.156$). There was one IUFD in the transaminitis group compared to zero in the non-transaminitis group.

Discussion:

Main Findings:

Our research is consistent with what has been previously published in non-pregnant populations infected with COVID-19. In our report, pregnant patients with transaminitis were generally sicker and more likely to require oxygen supplementation, intubation and ICU admission. A large meta-analysis found that ICU admission was predicted by elevations in ALT, AST, leukocyte count, lactate dehydrogenase (LDH) and procalcitonin.⁵ LDH was also seen in other studies of non-pregnant patients to be elevated with severe COVID-19 infections, serving as a predictor of poorer outcomes.^{6,7} While we did not evaluate the predictive value of LDH in this study, it would be an interesting follow-up to explore the predictive power of LDH in pregnant populations. Current studies also find that elevations in ALT and AST were more likely to be found in patients with severe COVID-19 infection compared to mild cases, suggesting that impaired hepatic function is likely representative of a sicker patient.⁶

Few studies have looked at liver injury in pregnant patients with COVID-19. In one study, a preeclampsia-like syndrome induced by COVID-19 was described in pregnant patients with severe COVID pneumonia, causing an elevation of liver enzymes to twice the normal concentrations.⁸ Another study examining clinical characteristics of 118 pregnant patients in Wuhan, China found 66.7% of patients with severe COVID-19 to have elevated AST compared to 16.5% of those without severe disease. In addition, they found 44.4% of patients with severe COVID-19 to have elevated ALT compared to 20.2% of those without severe disease.⁹ In contrast, another study in Wuhan looked specifically at characteristics of pregnant patients with COVID-19 and liver injury and found no correlation with severity of COVID-19.¹⁰ Specifically, they found 29.7% of the patients to have transaminitis and found no changes in this group of patients in regard to the maternal or neonatal outcomes. The only significant finding was elevated inflammatory markers of procalcitonin and IL-6 in the transaminitis group, suggesting that pregnant women with COVID-19 and liver injury have worse inflammation when compared to those without liver injury. Although not all outcome findings were consistent, both our study and prior studies suggest the importance of identifying transaminitis in pregnant patients infected with COVID-19, either to identify potential worse outcomes or inflammation.

There are many theories proposing how COVID-19 may cause transaminitis. These include the possibility of

direct insult of hepatocytes by the virus or by drug toxicity from interventions given to treat COVID-19.^{11,12} In contrast, other studies believe it is through activation of the ACE2 on cholangiocytes which indirectly affect hepatocytes.¹³ Earlier studies on other viruses suggest that transaminitis may not be due to direct viral insult, but rather due to the activation of the body's own innate immune response as is likely the case with Influenza A and H1N1.¹² While the exact etiology of the damage remains unknown, 2-11% of patients with COVID-19 are found to have coinciding liver abnormalities and 14-53% of cases are noted to have elevated AST and ALT.¹¹ Additionally, patients admitted to the ICU typically incur higher rates of liver dysfunction and elevated transaminases when compared to patients who did not require as high a level of care.^{11,15} Finally, patients with abnormal liver function have been seen to have longer length hospital stays, which has significant clinical implications.¹⁶

Strengths:

A strength of this study is that it adds another perspective to limited previous data on pregnant patients with COVID-19 and associated transaminitis.

Limitations:

The main limitations of our study include small sample size and the single-center location, which may limit generalizability. Additionally, patients who were less than 23 weeks of gestation were seen in the emergency department and not all were routinely tested for COVID-19. In addition, hepatic function panels were not routinely done in all admitted patients, which further limited our data and the number of patients who were included in the study. Finally, our hospital is a transfer center and thus not all of the patients deliver at our institution and delivery information could not be consistently obtained from other institutions, thus limiting our neonatal outcome data.

Conclusion:

This study revealed worse outcomes in pregnant patients infected with COVID-19 and with associated transaminitis. Due to limited data and overall information on COVID-19, it is difficult to determine if transaminitis serves as a predictor of worse outcomes, or if it is solely a marker of worsening disease. As more data becomes available on pregnant patients with COVID-19, it will be important to assess the effect of transaminitis on maternal and neonatal outcomes and if it is consistently predictive of poor outcomes. In the future, it will be crucial to determine if transaminitis can help determine clinical guidelines, such as timing of delivery.

Disclosure of Interest: All authors report no conflicts of interest.

Contribution to authorship : JAY, SJW, and GR conceived and designed the study. GR and SK supervised the study. SF was responsible for literature review. JAY, SJW and SF acquired and analyzed the data. JAY did the statistical analysis. JAY, SJW, SF, SK, and GR interpreted the data, were involved in preparing the manuscript and contributed to the critical revision of the manuscript. The corresponding author attests that all listed authors meeting authorship criteria. All authors accept responsibility for the paper as published.

Details of ethic approval : This study was approved by New York Medical College and Westchester Medical College Institutional Review Board (IRB), protocol #14296 on September 8th, 2020. Written consent was not required for this study because it was a case series and retrospective in nature. Therefore, the research involves no risk to the subjects the waiver or alteration will not adversely affect the rights and welfare of the subjects; the research could not practically be carried out without the waiver or alteration (i.e., it is impracticable to get consent of the subjects).

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